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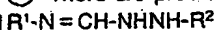
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(54) Carbazate derivatives, their production and use.

(57) There are provided carbazate derivatives of the formula:



wherein R^1 is a heterocyclic group; and R^2 is an esterified carboxyl group, and their salts, which are useful as AGE-formation inhibitory agents.

The derivatives or the salts can be produced by reacting compounds of the formula: $R^1-N=CH-R^3$ wherein R^1 is a heterocyclic group; and R^3 is a lower alkyl group, with a carbazic acid ester or its salt.

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Carbazate Derivatives, Their Production and Use

This invention relates to carbazic acid derivatives, or their salts, which exhibit inhibitory activity of AGE formation

In recent years, an increased attention is attracted to the glycosylated products of proteins through the nonenzymatic glycosylation, which is considered to be responsible for a variety of pathogenesis related to diabetes and atherosclerosis. The nonenzymatic glycosylation involves the chemical attachment of blood glucose to protein amino groups to form a Schiff base, followed by Amadori rearrangement to relatively stable ketoamine derivatives (1-amino-1-deoxyfructose), which cause changes in the structure and function of proteins. The resultant Amadori rearrangement products slowly dehydrate and rearrange themselves in several months to several years, and form irreversible advanced glycosylation end products (AGE). AGE are yellowish brown and fluorescent, and easily bind with adjacent proteins to form the crosslinks. The proteins, which have formed crosslinks through AGE formation, are thought to cause disturbances in various tissues. In diabetes, the nonenzymatic glycosylation of proteins increases in proportion to blood glucose levels, and this is regarded as one of the causes for diabetic complications [A. Cerami et al., "Metabolism" 28 (Suppl. 1) 431 (1979); V. M. Monnier et al., "The New England Journal of Medicine", 314, 403 (1986)]. The process is also considered to be responsible for aging. Senile cataract involves the AGE formation of crystalline or a protein existing in the crystalline lens of the eye. Furthermore, pathologic changes of atherosclerosis are associated with the AGE formation, as well. It has been confirmed that AGE are involved in the thickening of capillary basement membrane associated with aging and the thickening of glomerular basement membrane being responsible for renal insufficiency or failure [M. Brownlee et al. "Science", 232, 1629 (1986)].

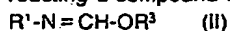
M. Brownlee et al reported that aminoguanidine can prevent the transformation of Amadori rearrangement products into AGE [M. Brownlee et al. "Science", 232, 1629 (1986)] and the compound is noted as a candidate which prevents from diseases associated with aging

In order to prevent and treat the diseases caused by AGE formation, there are called for the inhibitors of AGE formation. Since aminoguanidine as reported previously have not adequate inhibitory activity, more potent inhibitor of AGE formation is expected to be developed.

The present inventors, after extensive and intensive research on compounds being useful for the prevention of the above-mentioned diseases through inhibition of AGE formation, found that novel carbazic acid derivatives, as represented by the formula:



wherein R^1 is a heterocyclic group; and R^2 is an esterified carboxyl group, or their salts, are obtained by reacting a compound represented by the formula:



wherein R^1 is as defined in the above; and R^3 is a lower alkyl group with a carbazate or its salt, and that the carbazic acid derivatives, as represented by the formula: $R-N=CH-NHNH-R^2$ (III)

wherein R is a heterocyclic or aryl group; and R^2 is as defined in the above, or their salts, inclusive of the thus-obtained carbazic acid derivatives (I) or their salts, possess excellent inhibitory activity of AGE formation, and the findings have culminated into the present invention.

Referring to the above-described formulae, the heterocyclic group represented by R^1 and R includes heterocyclic groups having a linkage on the ring-constituting carbon atom, preferably 5-membered or 6-membered unsaturated heterocyclic rings containing 1 to 4 of nitrogen, oxygen sulfur, etc. as a ring constituting heteroatom or their condensed ring groups. Such heterocyclic groups show normally a molecular weight of 60 to 300, preferably 60 to 200. Specific examples of these heterocyclic groups as used include 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 4- or 8-quinolyl, 1-, 4- or 8-isoquinolyl, 2-, 4- or 5-pyrimidinyl, 3- or 4-pyridazinyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 4- or 5-(1,2,3-oxadiazolyl), 3- or 5-(1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 3- or 5-(1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, benzimidazolyl, benzothiazolyl, tetrahydrobenzthiazolyl, quinolyl, quinazolyl, pteridinyl or benzoxazolyl groups. In addition, the heterocyclic group represented by R^1 and R include those having 1 to 4 of the same or different substituents on the ring, and such substituents may be chosen for example from those as described in the following (i) to (x).

(i) Aromatic groups, such as C_6-14 aryl being exemplified by phenyl, naphthyl, tetrahydronaphthyl and anthryl, which may be substituted for example by 1 to 4 of alkyl groups, halogens and hydroxyl, nitro, acyl, acylamino, aminoalkylthio and aralkylthio groups.

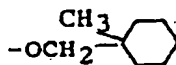
With reference to the above, preferably used as the alkyl group are, for example, C_1 to C_{10} straight-chain, branched or cyclic alkyl groups which may be substituted in arbitrary positions by 1 to 4 of halogen atoms (Br, Cl, I; etc.), and there are used, for example, methyl, trifluoromethyl, ethyl, 2,2,2-trifluoroethyl,

2,2,2-trichloroethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, pentyl, isopentyl, neopentyl, cyclopentyl, hexyl, cyclohexyl, heptyl, cycloheptyl, 2-methylcyclohexyl, octyl, nonyl, decyl, etc.

As examples of the halogen, there are used fluorine, chlorine, bromine and iodine, with chlorine being among others preferable.

- 5 As the hydroxyl group, there may be mentioned hydroxyl group and those having a suitable substituent, particularly the one used as a protective group for hydroxyl, in the hydroxyl group, such as alkoxy (for example, alkoxy having a number of carbon atoms of 1 to 8, being specifically exemplified by methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy, hexyloxy.

10



- 15 etc.), aralkyloxy (for example, phenyl-C₁₋₄ alkyloxy which may be substituted by 1 to 4 of halogens (Cl, Br, I, etc.), being specifically exemplified by benzyloxy, phenethyloxy, p-chlorobenzyloxy, etc.), acyloxy (for example, C₂ to C₄ alkanoyloxy, being specifically exemplified by acetyloxy, propionyloxy, n-butyryloxy, isobutyryloxy, etc.), aryloxy (for example, C₆ to C₁₀ aryloxy which may be substituted by 1 to 4 of halogens (Cl, Br, I, etc.), being specifically exemplified by phenoxy, p-chlorophenoxy, etc.) and the like.

- 20 As the acyl group, there may be used, for example, acyl groups consisting of C₁ to C₁₀ alkyl bonded to carbonyl (for example, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, etc.), acyl groups consisting of C₆ to C₁₀ aryl, which may be substituted by 1 to 4 of halogens (Cl, Br, I, etc.) or C₁ to C₄ alkoxy (methoxy, ethoxy, etc.), being attached to carbonyl (for example, benzoyl, p-chlorobenzoyl, p-methoxybenzoyl, naphthoyl, etc.) and the like.

- 25 As the acylamino group, there are used, for example, acylamino groups consisting of the acyl groups, which are exemplified above as the acyl group, being attached to amino groups.

- 30 As the amino group, there may be mentioned amino group and those substituted by 1 or 2 of C₁₋₁₀ alkyl groups, C₇₋₁₂ aralkyl groups and sulfonyl groups (for example, methylamino, ethylamino, propylamino, butylamino, pentylamino, cyclohexylamino, dimethylamino, dibutylamino, dihexylamino, benzylamino, N-benzyl-N-methylamino, N-(4-chlorobenzyl)-N-tosylamino, sulfonylamino, etc.) and the like.

- As the alkylthio or aralkylthio group, there may be mentioned, for example, groups consisting of the above-described alkyl or C₇ to C₁₂ aralkyl (benzyl, phenylethyl, etc.) groups bonded to a sulfur atom, which may be substituted by 1 to 4 of halogens (Cl, Br, I, etc.), and specifically, there are used methylthio, ethylthio, propylthio, butylthio, benzylthio, p-chlorobenzylthio, phenethylthio, etc.

- 35 (ii) Heterocyclic groups, such as 5-membered or 6-membered saturated or unsaturated heterocyclic groups containing at least one of heteroatoms, e.g. nitrogen oxygen and sulfur atoms, or their condensed heterocyclic groups (heteropolycyclic groups) (for example, pyridyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, morpholino, thiazolyl, isothiazolyl, benzoxazolyl, benzofuryl, benzothienyl, etc.), which may be substituted for example by 1 to 4 of alkyl groups, halogens, and hydroxyl, nitro, acyl, acylamino, amino, alkylthio and aralkylthio groups as mentioned above in the item (i).

- 40 (iii) Alkyl groups, such as those as mentioned above in the item (i), are used.

- (iv) Halogens, such as those as described above in the item (i), are employed.

- (v) Hydroxyl group, such as those as mentioned above in the item (i), are used.

- (vi) Nitro group.

- 45 (vii) Acyl groups, such as those as mentioned above in the item (i), are used.

- (viii) Acylamino groups, such as those as described above in the item (i), are employed.

- (ix) Amino groups, such as those as mentioned above in the item (i), are used.

- (x) Alkylthio groups, such as those as mentioned above in the item (i), are used.

- (xi) Aralkylthio groups, such as those as mentioned above in the item (i), are used.

- 50 Preferred examples of the heterocyclic group represented by R¹ and R include thiazolyl groups which may be substituted for example by 1 to 2 of lower alkyl groups (for example, C₁ to C₄ alkyl groups such as methyl, ethyl, propyl, n-butyl and i-butyl), C₆ to C₁₀ aryl groups (for example, phenyl, naphthyl and the like, which may be substituted by for example C₃ to C₆ cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl or phenyl-C₁₋₃ alkyloxy groups which may be substituted by 1 to 4 of halogens such as benzyloxy and 4-chlorobenzyloxy) and others.

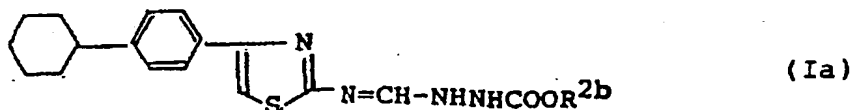
- 55 Referring now to the above-described formula (III), the aryl group represented by R includes, for example, C₆ to C₁₀ aryl groups, such as phenyl and naphthyl, which may be substituted by 1 to 4 of the substituents (i) to (xi) as mentioned above for the heterocyclic groups represented by R¹ and R. As the

preferable examples of the aryl group represented by R, there may be used phenyl groups which may be substituted for example by 1 to 2 of halogens (Cl, Br, I, etc.), C₁ to C₄ alkoxy groups (methoxy, ethoxy, etc.) and halogeno-C₁ to C₄ alkyl groups (chloromethyl, dichloroethyl, trifluoromethyl, etc.), and the like

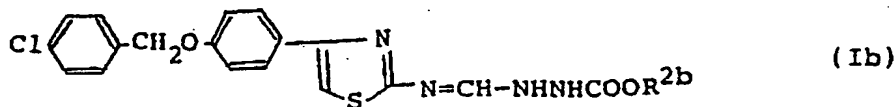
In the above formulae (I) and (III), R² represents an esterified carboxyl group, and includes for example groups represented by the formula -COOR^{2a} (wherein R^{2a} is an ester residue). As the ester residue represented by R^{2a}, there are used for example C₁ to C₁₀ alkyl, C₆ to C₁₄ aryl and phenyl-C₁ to C₄ alkyl groups, as mentioned above for the substituents in the heterocyclic groups represented by R₁ and R, which may be substituted by 1 to 3 of halogens (Cl, Br, F, etc.), C₁ to C₄ alkoxy (methoxy, ethoxy, propoxy, t-butoxy, n-butoxy, i-butoxy, etc.) and the like. Specific examples of the ester residue represented by R^{2a} include C₁ to C₈ alkyl groups, such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, cyclobutyl, pentyl, isopentyl, neopentyl, cyclopentyl, hexyl, cyclohexyl, heptyl, cyclohexylmethyl, cycloheptyl, 2-cyclohexylethyl and octyl, C₆ to C₁₄ aryl groups which may be substituted by a halogen or C₁-C₄ alkoxy such as phenyl, 4-chlorophenyl, 4-methoxyphenyl, 2-chlorophenyl and naphthyl and phenyl-C₁ to C₄ alkyl groups which may be substituted by 1 or 2 of the halogens or C₁-C₄ alkoxy groups, such as benzyl, phenethyl, 4-chlorobenzyl, 3,4-dimethoxyphenethyl and 3-(3-trifluorophenyl)propyl. Preferred examples of the ester residue represented by R^{2a} include C₁ to C₄ alkyl groups, such as methyl, ethyl, propyl, n-butyl and t-butyl, and C₆ to C₁₀ aryl group, such as phenyl.

As the lower alkyl group represented by R³ in the above formula (II), there are used preferably C₁ to C₄ alkyl groups such as methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl and t-butyl, and others.

Preferred examples of the novel carbazic acid derivatives (I) or their salts according to this invention include compounds represented by the formula:



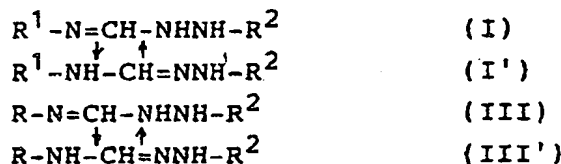
wherein R^{2b} is a C₁ to C₄ alkyl group, such as methyl, ethyl, propyl, n-butyl and t-butyl, or a C₆ to C₁₀ aryl group, such as phenyl, or their salts and compounds represented by the formula:



wherein R^{2b} is as defined above, or their salts.

The carbazic acid derivatives (I) and (III) can also be used in the form of salts, such as pharmaceutically acceptable salts to be produced with use of suitable acids by means of the conventional procedures. As the above acid salts, there are used, for example, mineral acid salts (hydrochloride, hydrobromide, sulfate, etc.), organic acid salts (succinate, maleate, fumarate, citrate, tartrate etc.), sulfonates (methanesulfonate, benzenesulfonate, toluenesulfonate, etc.) and the like, and these salts can all be produced by the known means.

The carbazic acid derivatives (I) and (III) are considered to be in equilibrium with their respective tautomers (I') and (III') of the following formulae:

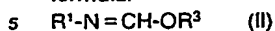


In this specification, (I') and (III') are understood to be included in (I) and (III), respectively, and are named in accordance with the formulae (I) and (III). Furthermore, the compounds (I) or (I') and (III) or (III') produce cis and trans isomers in terms of the double bond -N=CH or -CH=N-, and these individual

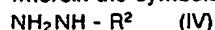
isomers and mixtures thereof are all included in the compounds (I) and (III), respectively.

The compounds (I) of this invention can be produced, for example, by the following procedure.

Thus, the compounds (I) or their salts can be produced by reacting a compound represented by the formula:



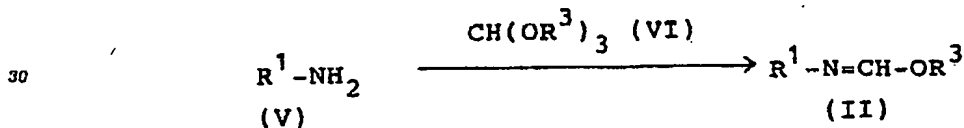
wherein the symbols are as defined in the above with a carbazic acid ester represented by the formula:



wherein R^2 is as defined in the above, or its salt (for example, the salts as mentioned above for the salts of the carbazic acid derivatives (I) and (III)).

10 In this reaction, the compounds (II) and (III) can be allowed to undergo an equimolar reaction, but either of these compounds may be used in slight excess. Also, the reaction may be carried out in a suitable solvent. As the solvent, there are used for example alcohols, such as methanol, ethanol, 2-propanol, butanol and 2-methoxyethanol, ethers, such as dioxane, tetrahydrofuran and dimethoxyethane, aromatic hydrocarbons, such as benzene, toluene and xylene, and halogenated hydrocarbons, such as chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, or solvent mixtures thereof. The used volume of the solvent is not specifically limited, unless it affects adversely the reaction, but is normally in the proportion of 0.1 to 10 liters against 1 mole of the compound (II), preferably 0.5 to 5 liters. The reaction temperature is normally in the range of $-20^\circ C$ to $100^\circ C$, preferably about $0^\circ C$ to $80^\circ C$. The reaction time ranges normally from 10 minutes to 50 hours, preferably from 0.5 to 10 hours. The carbazic acid derivative (I), or its salt, as obtained in the above manner can be isolated and purified by the known separation and purification procedures, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase inversion dissolution and chromatography. When the compound (I) or its salt consists of a mixture of isomers, they can also be separated in accordance with the conventional method.

25 The starting compound (II) to be used in this invention can be produced for example by the following procedure, as well.



35 wherein R^1 and R^3 are as defined in the above.

In this procedure, the amine derivative (V) is reacted with the ortho-ester (VI) to produce (II). This reaction may be carried out by heating (V) and (VI) in the presence or absence of a suitable solvent. As the said solvent, there are used for example ethers, such as dioxane, tetrahydrofuran and dimethoxyethane, aromatic hydrocarbons, such as benzene, toluene and xylene, ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide, dimethylsulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane or solvent mixtures thereof. The reaction temperature ranges normally from about $10^\circ C$ about $200^\circ C$, preferably from about $20^\circ C$ to about $150^\circ C$, while the reaction time is normally in the range of 10 minutes to 50 hours, preferably about 0.5 to 10 hours. The compound (II) obtained in this manner can be used as a starting material in this invention after being separated by the above-described known procedure, but can also be utilized, as the reaction mixture and without being separated, as a starting material in this invention.

The amine derivative (V) as used in the above procedure for the production of the compound (II) can be produced by the methods, or method similar thereto, as described in Chemical Abstracts, 53, 14089e (1959); Chemical Abstracts, 105, 221003s (1986); European Journal of Medicinal Chemistry, 16, 335 (1981); Shin-Jikken Kagaku Koza (New Discourse on Experimental Chemistry), 14, "Syntheses and Reactions of Organic Compounds [IV]" (1976) and others, while the ortho-ester (VI) can be prepared for example by the method, or methods similar thereto, as described in Shin-Jikken Kagaku Koza (New Discourse on Experimental Chemistry), 14, "Syntheses and Reactions of Organic Compounds [IV]" (1976).

55 The carbazic acid ester or its salt, which is other starting compound (IV) in the procedure of this invention, can be produced by the known method, or methods similar thereto, as described for example in Journal of Organic Chemistry, 37, 2413 (1972).

The carbazic acid derivatives (III) and their salts, because of their excellent AGE-formation inhibitory activities, can find application as drugs for human being and livestock, and are usable safely as an AGE-

formation inhibitory agent that acts to treat, cure and prevent a variety of diseases caused by the transformation of proteins into AGE.

The carbazic acid derivatives (III) or their salts can be processed solely or in combination with other active ingredients and after being incorporated with adjuvants, such as neutralizing agent, stabilizer and dispersant, if necessary, in accordance with the conventional procedure, and used in the forms of dosage preparations, such as capsules, tablets, powders, solutions suspensions or elixirs. These preparations can be administered parenterally (for example, through rectal administration) or orally

The carbazic acid derivatives (III) or their salts are admixed, as the case may be, with binders, such as syrup, gum arabic, gelatin, sorbitol, gum tragacanth and polyvinylpyrrolidone, fillers, such as lactose, sugars, corn starch, calcium phosphate, sorbitol and glycine, lubricants, such as magnesium stearate, talc, polyethylene glycol and silica, disintegrating agents, such as potato starch or wetting agents, such as sodium lauryl sulfate, and then, can be processed into pharmaceutical preparations for oral administration, such as tablets, capsules, granules and powders, in accordance with the conventional methods. Tablets, granules, etc. can be subjected to film coating by the procedures known per se, as well. Pharmaceutical preparations for oral administration may be employed in the forms of liquid preparations, such as aqueous or oil-borne suspensions, solutions, emulsions and elixirs.

Pharmaceutical preparations for rectal administration containing the carbazic acid derivatives (III) or their salts are produced in accordance with the conventional method by mixing a suppository base and additives with the carbazic acid (III) or its salts and then forming the mixture for example into oily solid suppositories, semi-solid ointment-like suppositories and capsule suppositories having a liquid composition filled into soft capsules. The carbazic acid derivative (III) or its salt is formulated normally at a ratio chosen from the range of about 0.5 to 50 weight %, but the formulation proportion is in no way limited to the range. In this invention, other non-ionic surfactants, such as polyoxyethylene fatty acid esters and polyoxyethylene higher alcohol ethers, may be added simultaneously to the preparations or anionic surfactants can also be formulated for the purpose of enhancing the bioavailability of the carbazic acid derivative (III) or its salt or for the purpose of controlling its absorption rate. In addition, there can be formulated or added a variety of salts or stabilizers in order to increase solubility or stability of the carbazic acid derivative (III) or its salt. Further, dispersing agents, preservatives, etc. can also be added, if necessary from the standpoint of pharmaceutical processing.

Also, other ingredients, such as known antioxidants, preservatives, lubricants, viscosity-increasing agents of flavors, may be admixed into these pharmaceutical preparations in accordance with the conventional methods. Furthermore, other active ingredients can also be incorporated into the pharmaceutical preparations to produce the preparations which can exhibit desired inhibitory activity of AGE formation.

The carbazic acid derivatives (III) or their salts can be used as an AGE-formation inhibitory agent, for example, in the treatment and prevention of diabetic complications, senile cataracts, atherosclerosis, glomerular basement membrane thickening, etc. in human being and other mammals. The daily dose of the carbazic acid derivatives (III) or their salts vary depending upon the conditions and body weight of patients, the route of administration and the like, but the compounds are administered parenterally to human adults in the daily dose of about 0.05 to 80 mg as an active ingredient (the carbazic acid derivative (III) or its salt) per kg body weight, preferably about 0.1 to 10 mg, and are suitably given through rectal administration as divided into twice to four times a day. The compounds are suitably administered orally to adults in the dose of about 0.5 to 100 mg as an active ingredient (the carbazic acid derivative (III) or its salt) per kg body weight as divided into once to three times a day.

It is to be further added that the carbazic acid derivative (III) or its salts allow excellent distribution within the body and are substantially free from side-effects, thereby constituting the ideal AGE-formation inhibitory agent that can demonstrate the therapeutic and preventive effects against diseases brought about by the transformation of proteins into AGE.

Experiment Example

The production and measurement of advanced glycosylation end products (AGE) were carried out according to the method of M. Brownlee et al. [Science, 232, 1629 (1986)]. Namely, Bovine serum albumin (fraction V, manufactured by Wako Pure Chemical of Japan, 20 %), D-glucose (100 mM) and sodium azide (3 mM) were dissolved in 0.5 M-phosphate buffer solution (pH 7.4) to prepare a reaction solution (control). Test compounds (the compounds as obtained in the below-described examples), after being dissolved in dimethylsulfoxide, were added to the reaction solution at a concentration of 1 mM, respectively. These

solutions were incubated at 37 °C for 7 days. Before and after incubation, the solutions were diluted with phosphate buffer to measure of fluorescence at the excitation and emission wavelengths of 370 nm 440 nm, respectively, using a spectrofluorimeter (Model RF-510 of Shimazu Seisakusho). Changes (ΔF) in fluorescence were used to calculate the AGE production ratios (%) by the following equation, whereby the reaction

5 solution without D-glucose contained was used as a blank. The results are shown in Table 1.

$$\text{AGE production ratio} = [\Delta F(t) - \Delta F(b) / \Delta F(c) - \Delta F(b)] \times 100$$

Where ;

$\Delta F(t)$ is ΔF found for test compounds,

$\Delta F(b)$ is ΔF found for blind test

10 $\Delta F(c)$ is ΔF found for control.

Table 1:

Compound in Example No.	AGE production ratio (%) against control value)
1	68
2	64
3	59
4	22
5	47
9	46
10	43
11	61
14	56
17	66
26	54
27	45
28	63
31	66
33	47
34	41
41	0

Table 1 reveals that AGE formed after addition of the carbazic acid derivatives (III) or their salts to the reaction solution was extremely lower than found without addition of the same (AGE formation ratio was taken as 100 %), and consequently demonstrates clearly that the carbazic acid derivatives (III) or their salts possess excellent AGE-formation inhibitory activity.

Since the carbazic acid derivatives (III) or their salts exhibit excellent AGE-formation inhibitory activity, this invention can provide novel AGE-formation inhibitory agents that are useful for the prevention and treatment of diseases being brought about by the glycosylated proteins into AGE.

The reference example and examples are described in the following to illustrate this invention more specifically. The melting points (mp) to be given throughout the examples are as determined by the hot plate method and not corrected.

Reference Example 1

A mixture of 2-amino-4-(4-cyclohexylphenyl)thiazole hydrochloride (1.0 g) and triethyl orthoformate (5 ml) was stirred at 130 °C for 1 hour. The reaction mixture was concentrated under reduced pressure, and to the remaining crystals was added hexane, followed by filtration. The filtrate was concentrated to give crystals of 4-(4-cyclohexylphenyl)-2-ethoxymethyleneaminothiazole (1.02 g, yield of 95.6 %). Recrystallization from diethyl ether/hexane produced yellowish prisms, mp of 84 to 85 °C.

Elemental analysis, for $C_{18}H_{22}N_2OS$

Calcd.:	C, 68.76; H, 7.05; N, 8.91
Found :	C, 68.73; H, 7.06; N, 8.93

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Example 1

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A mixture consisting of 4-(4-cyclohexylphenyl)-2-ethoxymethyleneaminothiazole (500 mg), ethyl carbazate (170 mg) and ethanol (10 ml) was stirred under ice-cooling for 1 hour and then at room temperature (about 15°C) for 18 hours. The reaction mixture was concentrated under reduced pressure, and the crystals were collected by filtration with hexane to give ethyl 3-[4-(4-cyclohexylphenyl)-2-thiazolyliminomethyl]-carbazate (515 mg, yield of 87 %). Recrystallization from dimethylformamide-water produced colorless prisms, mp of 188 to 189°C. Elemental analysis, for $C_{19}H_{24}N_4O_2S$

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Calcd.:	C, 61.27; H, 6.49; N, 15.04
Found :	C, 61.32; H, 6.52; N, 14.97

25

Example 2

A mixture of 2-amino-4-(5,6,7,8-tetrahydro-2-naphthyl) thiazole (1.5 g) and ethyl orthoformate (30 ml) was stirred at 130 to 135°C for 2 hours and concentrated under reduced pressure. The residue was dissolved in ethanol (20 ml), and the solution was admixed with ethyl carbazate (680 mg), followed by stirring at room temperature (about 15°C) for 6 hours. The solvent was evaporated off, and the remaining crystals were collected by filtration with diisopropyl ether to give ethyl 3-[4-(5,6,7,8-tetrahydro-2-naphthyl)-2-thiazolyliminomethyl] carbazate (1.84 g, yield of 82 %). Recrystallization from ethanol produced colorless prisms, mp of 134 to 135°C.

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Elemental analysis, for $C_{17}H_{20}N_4O_2S$

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Calcd.:	C, 59.28; H, 5.85; N, 16.29
Found :	C, 59.61; H, 5.91; N, 16.05

45

Examples 3 through 42

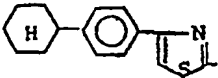
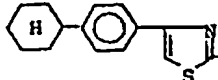
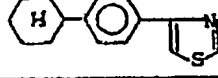

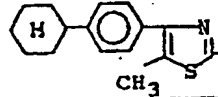
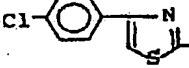
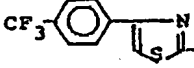
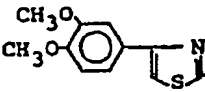
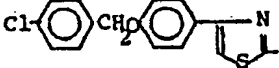
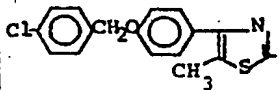
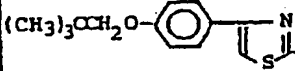
By following the same procedure as described in Example 2, there were obtained the compounds as shown in Table 2.

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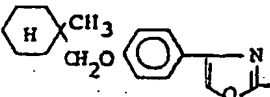
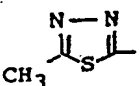
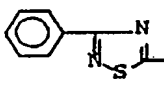
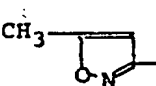
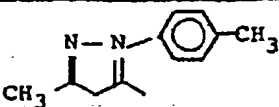

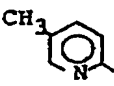
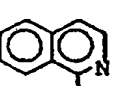
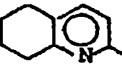
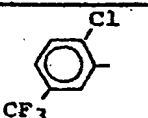
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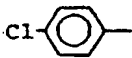
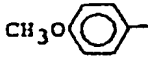

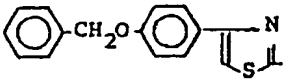
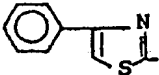
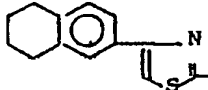
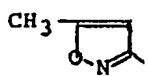
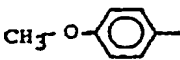
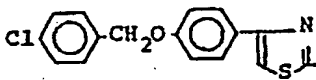
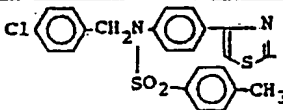
Table 2:



Example No.	R	R ^{2a}	Yield %	Recrystallization solvent	mp °C
3		CH ₃	85.1	DMF-H ₂ O	194 - 195
4		tert-C ₄ H ₉	87.8	DMF-H ₂ O	203-204
5			65.4	DMF-H ₂ O	210-212
6		C ₂ H ₅	57.1	CH ₂ Cl ₂ -EtOH	196-197
7		C ₂ H ₅	74.7	DMF-H ₂ O	196-197
8		C ₂ H ₅	88.6	DMF-H ₂ O	198-199
9		C ₂ H ₅	70.8	EtOH-Et ₂ O	136-137
10		C ₂ H ₅	57.1	CHCl ₃ -EtOH	212-213
11		C ₂ H ₅	82.8	CH ₂ Cl ₂ -EtOH	199-200
12		C ₂ H ₅	81.8	CH ₂ Cl ₂ -i-Pr ₂ O	165-166

Example No.	R	R ^{2a}	Yield %	Recrystallization solvent	mp °C
13		C ₂ H ₅	90.8	CH ₂ Cl ₂ -EtOH	200-201
14		C ₂ H ₅	68.0	CH ₂ Cl ₂ -EtOH	182-183
15		C ₂ H ₅	76.4	CH ₂ Cl ₂ -EtOH	189-190
16		C ₂ H ₅	58.7	CHCl ₃ -MeOH	211-212
17		C ₂ H ₅	37.7	CH ₂ Cl ₂ -EtOH	185-186
18		tert-C ₄ H ₉	67.1	CH ₂ Cl ₂ -EtOH	173-174
19		tert-C ₄ H ₉	80.9	CH ₂ Cl ₂ -EtOH	187-188
20		tert-C ₄ H ₉	79.4	CH ₂ Cl ₂ -EtOH	213-214
21		C ₂ H ₅	69.9	—	oil ¹⁾
22		C ₂ H ₅	73.0	Me ₂ CO-iPr ₂ O	146-147

Example No.	R	R ^{2a}	Yield %	Recrystallization Solvent	mp °C
23		C ₂ H ₅	47.5	CH ₂ Cl ₂ -iPr ₂ O	142-143
24		C ₂ H ₅	40.3	DMSO-H ₂ O	207-208
25		C ₂ H ₅	80.1	CHCl ₃ -EtOH	215-216
26		C ₂ H ₅	61.9	CH ₂ Cl ₂ -EtOH	159-160
27		C ₂ H ₅	64.4	CH ₂ Cl ₂ -hexane	103-104
28		C ₂ H ₅	31.4	CH ₂ Cl ₂ -EtOH	184-185
29		C ₂ H ₅	41.2	Me ₂ CO-iPr ₂ O	153-154
30		C ₂ H ₅	68.1	CH ₂ Cl ₂ -EtOH	180-181
31		C ₂ H ₅	56.9	CH ₂ Cl ₂ -EtOH	200-201
32		C ₂ H ₅	71.4	CHCl ₃ -iPr ₂ O	167-168

Example No.	R	R ₂ a	Yield %	Recrystallization solvent	mp °C
5 33		C ₂ H ₅	67.0	EtOH-H ₂ O	167-168
10 34		C ₂ H ₅	84.4	CH ₂ Cl ₂ -iPr ₂ O	131-132
15 35		C ₂ H ₅	67.2	CH ₂ Cl ₂ -iPr ₂ O	112-114
20 36		C ₂ H ₅	75.5	CH ₂ Cl ₂ -EtOH	187-188
25 37		C ₂ H ₅	85.3	CH ₂ Cl ₂ -EtOH	183-184
30 38		tert-C ₄ H ₉	68.0	CH ₂ Cl ₂ -EtOH	192-193
35 39		tert-C ₄ H ₉	55.7	CH ₂ Cl ₂ -EtOH	184-185
40 40		tert-C ₄ H ₉	53.1	CH ₂ Cl ₂ -iPr ₂ O	143-144
45 41		tert-C ₄ H ₉	91.4	CH ₂ Cl ₂ -EtOH	219-221
50 42		C ₂ H ₅	88.1	—	oil ²⁾

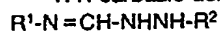
1) NMR (δ ppm in CDCl_3): 1.28(3H, t, $J=7$ Hz), 1.0-2.1(10H, m),
2.3-2.7(4H, m), 4.28(2H, q, $J=7$ Hz),
7.5-7.6(6H, m)

2) NMR (δ ppm in d_6 -DMSO): 1.21 (3H, t, $J=7$ Hz),
2.41(3H, s), 4.09(2H, q, $J=7$ Hz),
4.78(2H, broad s), 7.05(2H, d, $J=8.5$
Hz), 7.25-7.8(11H, m), 8.09(1H,
broad s), 10.25(1H, broad s),
10.76 (1H, broad s)

In the above Table, "DMF", "DMSO", "EtOH", "i-Pr₂O", "MeOH" and "Me₂CO" stand for dimethylformamide, dimethylsulfoxide, diisopropyl ether, methanol and acetone, respectively.

Claims

1. A carbazic acid derivative of the formula:



wherein R^1 is a heterocyclic group; and R^2 is an esterified carboxyl group, or its salt.

2. A carbazic acid derivative or its salt according to Claim 1, wherein R^1 is a heterocyclic group having a molecular weight of 60 to 300.

3. A compound according to Claim 1, wherein the heterocyclic group is a 5- or 6-membered unsaturated heterocyclic ring containing 1 to 4 of nitrogen, oxygen and sulfur as a ring-constituting heteroatom or its condensed ring which may be substituted with 1 to 4 of the same or different substituents chosen from (i) a C_6-14 aryl which may be substituted by 1 to 4 of (a) a C_1 to C_{10} straight-chain, branched or cyclic alkyl group which may be substituted by 1 to 4 of halogen atoms, (b) halogen, (c) hydroxyl, C_1-4 alkoxy, phenyl- C_1-4 alkyloxy which may be substituted by 1 to 4 of halogen atoms, C_2-4 alkanoyloxy, or C_6-10 aryloxy which may be substituted by 1 to 4 of halogen atoms, (d) nitro, (e) C_1-10 alkylcarbonyl, or C_6-10 arylcarbonyl wherein the aryl group may be substituted by 1 to 4 of halogen atoms, and C_1-4 alkoxy, (f) acylamino wherein the acyl group is as defined above in (e), (g) amino which may be substituted by 1 or 4 of C_1-10 alkyl, C_7-10 aralkyl and sulfonyl group, or (h) C_1 to C_{10} straight-chain, branched or cyclic alkylthio or C_7 to C_{12} aralkylthio which may be substituted by 1 to 4 of halogen atoms, (ii) a 5- or 6-membered saturated or unsaturated heterocyclic group containing at least one of nitrogen, oxygen and sulfur atoms or its condensed heterocyclic group which may be substituted by 1 to 4 of the groups (a) to (h) as mentioned above in (i), (iii) C_1 to C_{10} straight-chain, branched or cyclic alkyl group which may be substituted by 1 to 4 of halogen atoms, (iv) a halogen atom, (v) a hydroxyl, C_1-4 alkoxy, phenyl- C_1-4 alkyloxy which may be substituted by 1 to 4 of halogen atoms, C_2-4 alkanoyloxy, or C_6-10 aryloxy which may be substituted by 1 to 4 of halogen atoms, (vi) nitro, (vii) a C_1-10 alkylcarbonyl, or C_6-10 arylcarbonyl wherein the aryl group may be substituted by 1 to 4 of halogen atoms and C_1-4 alkoxy, (viii) acylamino wherein the acyl group is as defined above in (vii), (ix) an amino which may be substituted by 1 or 2 of C_1-10 alkyl, C_7-12 aralkyl and sulfonyl group, (x) a C_1 to C_{10} straight-chain, branched or cyclic alkylthio group which may be substituted by 1 to 4 of halogen atoms and (xi) a C_7 to C_{12} aralkylthio which may be substituted by 1 to 4 of halogen atoms.

4. A compound according to Claim 1, wherein the heterocyclic group is a thiazolyl group which may be substituted by 1 to 2 of (i) a C_1 to C_4 alkyl group and (ii) a C_6 to C_{10} aryl group which may be substituted by a C_3 to C_6 cycloalkyl group or a phenyl- C_1-3 alkyloxy group which may be substituted by 1 to 4 of halogen atoms.

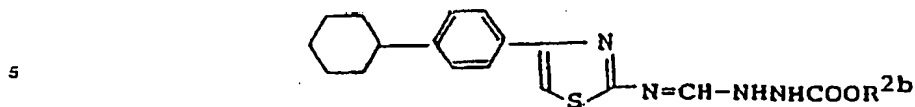
5. A compound according to Claim 1, wherein the esterified carboxyl group is a group of the formula: $-\text{COOR}^{2a}$ wherein R^{2a} is an ester residue.

6. A compound according to Claim 5, wherein the ester residue is a C_1 to C_{10} alkyl, C_6 to C_{14} aryl or phenyl- C_1 to C_4 alkyl group which may be substituted by 1 to 3 of halogen atoms and C_1 to C_4 alkoxy.

7. A compound according to Claim 5, wherein the ester residue is a C_1 to C_4 alkyl or C_6 to C_{10} aryl group.

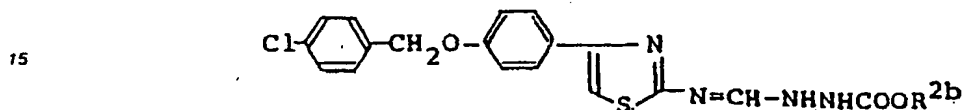
8. A compound according to Claim 1, wherein the salt is a pharmaceutically acceptable salt.

9. A compound according to Claim 1, which is a compound of the formula;



10 wherein R^{2b} is a C₁ to C₄ alkyl group or a C₆ to C₁₀ aryl group, or a pharmaceutically acceptable salt thereof

10. A compound according to Claim 1, which is a compound of the formula;



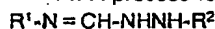
20 wherein R^{2b} is a C₁ to C₄ alkyl group or a C₆ to C₁₀ aryl group, or a pharmaceutically acceptable salt thereof.

11 A compound according to Claim 1, which is tert-butyl 3-[4-[4-(4-chlorobenzoyloxy)phenyl]-2-thiazolyliminomethyl]carbazate.

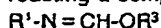
25 12. A compound according to Claim 1, which is ethyl 3-[4-(4-cyclohexylphenyl)-2-thiazolyliminomethyl]carbazate.

13. A carbazic acid derivative or its salt according to Claim 1, wherein R¹ is a thiazolyl group which may be substituted by cyclohexylphenyl or cyclobenzoyloxyphenyl.

14. A process for producing a carbazic acid derivative of the formula:

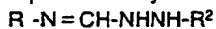


30 wherein R¹ is as defined hereinafter; and R² is an esterified carboxyl group, or its salt, which comprises reacting a compound represented by the formula:



wherein R¹ is a heterocyclic group; and R³ is a lower alkyl group with a carbazic acid ester or its salt.

35 15. An AGE-forming inhibitory agent which contains an effective amount of a carbazic acid derivative represented by the formula:



wherein R is a heterocyclic or aryl group; and R² is a esterified carboxyl group, or its pharmaceutically acceptable salt, together with a suitable carrier or carriers.

40 16. The use of a carbazic acid derivative of the formula R-N=CH-NHNH-R² wherein R is a heterocyclic or aryl group and R² is an esterified carboxyl group or a pharmaceutically acceptable salt thereof in the preparation of an AGE-formation inhibitory agent.